Statements under 37 C.F.R. §1.173(c)

The following statements are made pursuant to the requirements of 37 C.F.R. §1.173(c). Patent claims 1-4 have been cancelled without prejudice toward the continuation of prosecution in a continuing application. Added claims 5-176 and 178-209 have also been cancelled without prejudice. Claims 177 and 210-228 are the only claims now pending in the case.

Pursuant to 37 C.F.R. §1.173(c), the following is an explanation of the support in the disclosure of the patent for the changes made to the claims by the present amendment.

Claims 210-216, 218-220, 222-226 and 228 have been amended to specify that the genetically engineered antibody or the fragment thereof, or the human monoclonal antibody or fragment thereof, all "bind beta-amyloid". This was made at the suggestion of the examiner during a telephone interview. Support for the fact that the antibody must bind to the β-amyloid is found in the specification at:

Column 3, lines 45-47:

> These anti-aggregation molecules are able to bind to a native target molecule epitope with a high binding constant …

Column 5, lines 30-32:

> The antibodies … must bind to an epitope on the target molecule which is a region responsible for folding or aggregation.

Column 6, lines 7-14:

> A method of treating a protein aggregation disease intracellularly includes the steps of preparing (Haber. 1992; Harlow & Lane, 1988) or selecting an anti-aggregation molecule, such as a monoclonal antibody, genetically engineered monoclonal antibody fragment or peptide that mimics the binding site of an antibody, that binds to an aggregating protein which is the cause of a disease and which prevents aggregation and yet allows the protein to be bio-active.

Column 6, lines 21-26:

> In the preferred embodiment the human monoclonal antibody that binds to an aggregating protein and which prevents aggregation is utilized. In a further preferred embodiment the monoclonal antibody is an anti-β-amyloid and is designated AMY-33 which recognizes amino acids 1-28 of β-amyloid.

Column 16, lines 5-6:

> Binding of mAb AMY-33 to βA4 prevents self-aggregation of the β-amyloid, … .

All underlined emphasis is added.

Claims 210-214, 219-220 and 222-224 have been amended to change the language from "is obtainable using a peptide consisting of residues 1-28 of β-amyloid as an immunogen" to read, "is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of β-amyloid." This makes it clear that immunogenic peptides other than that consisting of residues 1-28 of β-amyloid are not present in the immunogen. This change was made in an attempt to eliminate the unduly broad interpretation of the previous

claim language and make sure that the claim reads only on that which applicant intended to claim in the first place.

Support for the fact that the immunogen consists of a peptide consisting of residues 1-28 of human beta-amyloid may be found in the present specification at -

Column 11, lines 33-37:

> In general, monoclonal antibodies may be prepared against a synthetic peptide based on the sequence, or prepared recombinantly by cloning techniques or the natural gene product and/or portions thereof may be isolated and used as the immunogen. [Note it does not say "used as an immunogen"; it says "used as the immunogen." Thus the immunogen consists of this natural gene product or portion thereof.]

Column 15, lines 35-38:

> … mAb AMY 33 (Stern et al., 1990), purchased from Zymed, San Francisco, Calif., USA, raised against peptides … 1-28 … of the β-amyloid. [Note that this establishes that peptides 1-28 of the β-amyloid is an example of the immunogen referred to in the previous quotation.]

REMARKS

Claims 177 and 210-228 presently appear in this case. No claims have been allowed. The official action of December 10, 2009, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a therapeutic composition that comprises a pharmaceutical formulation of a pharmaceutically acceptable carrier and a human or genetically-engineered monoclonal antibody or antibody binding fragment thereof. The antibody is one that binds β-amyloid and either inhibits aggregation of β-amyloid, maintains the solubility of soluble β-amyloid, or disaggregates an aggregate of β-amyloid. When the antibody is one that inhibits aggregation of β-amyloid or maintains the solubility of soluble β-amyloid, it does so at least to the extent that monoclonal antibody AMY-33 does so. The genetically-engineered antibody is obtained from DNA encoding a monoclonal antibody that either recognizes an epitope within residues 1-28 of β-amyloid or is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of β-amyloid. The human monoclonal antibody must be one that is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of β-amyloid. The invention also relates to a method for making such a pharmaceutical

formulation by first selecting the monoclonal antibody and then genetically engineering it prior to incorporating it into a pharmaceutical formulation.

Copy of Claims in Conventional Amended Format

MPEP §1453.V.D. states with respect to the amendment of new claims:

> Although the presentation of the amended claim does not contain any indication of what is changed from the previous version of the claim, applicant must point out what is changed in the "Remarks" portion of the amendment.

Claim 177, 217, 221 and 227 have not been amended by the present amendment. All of claims 210-216, 218-220, 222-226 and 228 are previously presented new claims in the sense that they were not present in the patent as issued and are being amended by the present amendment. So that the examiner can see how the claims are being amended from the previous version of these claims, the following is a recitation of all of the pending claims, including the amended claims, shown in the conventional amended format:

1-176 (Cancelled).

177 (Previously Presented). The therapeutic composition of claim 210 or 211, wherein said genetically-engineered monoclonal antibody is a single-chain antibody.

178-209 (Cancelled).

210 (Currently Amended). A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a genetically-engineered antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or

(b) a fragment of the genetically-engineered antibody of (a) that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33,

wherein said genetically-engineered antibody is obtained by genetically engineering the DNA encoding a monoclonal antibody that

(i) binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and

(ii) is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of beta-amyloid ~~as an immunogen~~; and

wherein said antibody or fragment is not conjugated with a detectable moiety.

211 (Currently Amended). The therapeutic composition of claim 210, wherein said genetically-engineered

antibody of (2)(a) binds human beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or said fragment of (2)(b) binds human beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and said genetically-engineered antibody of (2)(a) is obtained by genetically engineering the DNA encoding a monoclonal antibody that binds human beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33 and said monoclonal antibody is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of human beta-amyloid ~~as an immunogen~~.

212 (Currently Amended). A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a human monoclonal antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or

(b) a fragment of the human monoclonal antibody of (a) that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-

amyloid to an extent at least as great as that obtainable with antibody AMY-33,

wherein said human monoclonal antibody is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of beta-amyloid ~~as an immunogen~~.

213 (Currently amended). The therapeutic composition of claim 212, wherein said human monoclonal antibody of (2)(a) binds beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or said fragment of (2)(b) binds beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and wherein said human monoclonal antibody of (a) is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of human beta-amyloid ~~as an immunogen~~.

214 (Currently Amended). A method of making a therapeutic composition comprising (1) a pharmaceutically acceptable carrier and (2)(a) a genetically-engineered antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or (b) a fragment of the genetically-engineered antibody of (a), which fragment binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the

solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, said method comprising:

selecting a monoclonal antibody that

(i) binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and

(ii) is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of beta-amyloid ~~as an immunogen~~;

genetically engineering the DNA encoding said selected monoclonal antibody so as to produce a genetically-engineered antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or a fragment of a genetically engineered antibody, which fragment binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33; and

formulating said genetically engineered monoclonal antibody or fragment with a pharmaceutical carrier into a pharmaceutical formulation that is a therapeutic composition.

215 (Currently Amended). A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a genetically-engineered antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or

(b) a fragment of the genetically-engineered antibody of (a) that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33,

wherein said genetically-engineered antibody is obtained by genetically engineering the DNA encoding a monoclonal antibody that

(i) binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and

(ii) recognizes an epitope within residues 1-28 of beta-amyloid, and

wherein said antibody or fragment is not conjugated with a detectable moiety.

216 (Currently Amended). The therapeutic composition of claim 215, wherein said genetically-engineered antibody of (2)(a) binds beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or said fragment of (2)(b)

binds beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and said genetically-engineered antibody of (2)(a) is obtained by genetically engineering the DNA encoding a monoclonal antibody that binds beta-amyloid and inhibits aggregation of human beta-amyloid or maintains the solubility of soluble human beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33 and said monoclonal antibody recognizes an epitope within residues 1-28 of human beta-amyloid.

217 (Previously Presented). The therapeutic composition of claim 215 or 216, wherein said genetically-engineered monoclonal antibody is a single-chain antibody.

218 (Currently Amended). A method of making a therapeutic composition comprising (1) a pharmaceutically acceptable carrier and (2)(a) a genetically-engineered antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or (b) a fragment of the genetically-engineered antibody of (a), which fragment binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, said method comprising:

selecting a monoclonal antibody that

(i) binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and

(ii) recognizes an epitope within residues 1-28 of beta-amyloid;

genetically engineering the DNA encoding said selected monoclonal antibody so as to produce a genetically-engineered antibody that binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33, or a fragment of a genetically engineered antibody, which fragment binds beta-amyloid and inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33; and

formulating said genetically engineered monoclonal antibody or fragment with a pharmaceutical carrier into a pharmaceutical formulation that is a therapeutic composition.

219 (Currently Amended). A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a genetically-engineered antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or

(b) a fragment of the genetically-engineered antibody of (a) that binds beta-amyloid and disaggregates an aggregate of β-amyloid,

wherein said genetically-engineered antibody is obtained by genetically engineering the DNA encoding a monoclonal antibody that

(i) binds beta-amyloid and disaggregates an aggregate of β-amyloid and

(ii) is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of beta-amyloid ~~as an immunogen~~, and

wherein said antibody or fragment is not conjugated with a detectable moiety.

220 (Currently Amended). The therapeutic composition of claim 219, wherein said genetically-engineered antibody of (2)(a) binds beta-amyloid and disaggregates an aggregate of human β-amyloid, or said fragment of (2)(b) binds beta-amyloid and disaggregates an aggregate of human β-amyloid, and said genetically-engineered antibody of (2)(a) is obtained by genetically engineering the DNA encoding a monoclonal antibody that binds beta-amyloid and disaggregates an aggregate of human β-amyloid and said monoclonal antibody is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of human beta-amyloid ~~as an immunogen~~.

221 (Previously Presented). The therapeutic composition of claim 219 or 220, wherein said genetically-engineered monoclonal antibody is a single-chain antibody.

222 (Currently Amended). A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a human monoclonal antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or

(b) a fragment of the human monoclonal antibody of (a) that binds beta-amyloid and disaggregates an aggregate of β-amyloid,

wherein said human monoclonal antibody is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of beta-amyloid ~~as an immunogen~~.

223 (Currently Amended). The therapeutic composition of claim 222, wherein said human monoclonal antibody of (2)(a) binds beta-amyloid and disaggregates an aggregate of human β-amyloid, or said fragment of (2)(b) binds beta-amyloid and disaggregates an aggregate of human β-amyloid, and wherein said human monoclonal antibody of (a) is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of human beta-amyloid ~~as an immunogen~~.

224 (Currently Amended). A method of making a therapeutic composition comprising (1) a pharmaceutically acceptable carrier and (2)(a) a genetically-engineered

antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or (b) a fragment of the genetically-engineered antibody of (a), which fragment binds beta-amyloid and disaggregates an aggregate of β-amyloid, said method comprising:

selecting a monoclonal antibody that

(i) binds beta-amyloid and disaggregates an aggregate of β-amyloid, and

(ii) is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of beta-amyloid ~~as an immunogen~~;

genetically engineering the DNA encoding said selected monoclonal antibody so as to produce a genetically-engineered antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or a fragment of a genetically engineered antibody, which fragment binds beta-amyloid and disaggregates an aggregate of β-amyloid; and

formulating said genetically engineered monoclonal antibody or fragment with a pharmaceutical carrier into a pharmaceutical formulation that is a therapeutic composition.

225 (Currently Amended). A therapeutic composition, comprising:

a pharmaceutical formulation comprising

(1) a pharmaceutically acceptable carrier and

(2)(a) a genetically-engineered antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or

(b) a fragment of the genetically-engineered antibody of (a) that binds beta-amyloid and disaggregates an aggregate of β-amyloid,

wherein said genetically-engineered antibody is obtained by genetically engineering the DNA encoding a monoclonal antibody that

(i) binds beta-amyloid and disaggregates an aggregate of β-amyloid and

(ii) recognizes an epitope within residues 1-28 of beta-amyloid, and

wherein said antibody or fragment is not conjugated with a detectable moiety.

226 (Currently Amended). The therapeutic composition of claim 225, wherein said genetically-engineered antibody of (2)(a) binds beta-amyloid and disaggregates an aggregate of human β-amyloid, or said fragment of (2)(b) binds beta-amyloid and disaggregates an aggregate of human β-amyloid, and said genetically-engineered antibody of (2)(a) is obtained by genetically engineering the DNA encoding a monoclonal antibody that binds beta-amyloid and disaggregates an aggregate of human β-amyloid and said monoclonal antibody recognizes an epitope within residues 1-28 of human beta-amyloid.

227 (Previously Presented). The therapeutic composition of claim 225 or 226, wherein said genetically-engineered monoclonal antibody is a single-chain antibody.

228 (Currently Amended). A method of making a therapeutic composition comprising (1) a pharmaceutically acceptable carrier and (2)(a) a genetically-engineered antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or (b) a fragment of the genetically-engineered antibody of (a), which fragment binds beta-amyloid and disaggregates an aggregate of β-amyloid, said method comprising:

selecting a monoclonal antibody that

(i) binds beta-amyloid and disaggregates an aggregate of β-amyloid, and

(ii) recognizes an epitope within residues 1-28 of beta-amyloid;

genetically engineering the DNA encoding said selected monoclonal antibody so as to produce a genetically-engineered antibody that binds beta-amyloid and disaggregates an aggregate of β-amyloid, or a fragment of a genetically engineered antibody, which fragment binds beta-amyloid and disaggregates an aggregate of β-amyloid; and

formulating said genetically engineered monoclonal antibody or fragment with a pharmaceutical carrier into a pharmaceutical formulation that is a therapeutic composition.

Telephone Interviews

On May 7, 2010, a telephone conference was held between Examiner Ballard and the undersigned. The undersigned requested a formal telephone interview on Monday, May 10,

2010, to discuss whether proposed amendments to the claims would be entered for the purpose of appeal. A copy of the proposed amendments to the claims, which amendments were the same as presented herein, was emailed to Examiner Ballard and her mentor, Examiner Kemmerer. Examiner Ballard said that she would be in touch with Examiner Kemmerer and be back to me on Monday. On May 10, 2010, the undersigned received a telephone call from Examiner Stucker advising that Examiner Ballard had commenced a maternity leave but that she had asked him to advise the undersigned that she had discussed the proposed amendment with Examiner Kemmerer and had decided that such an amendment would be entered after Final Rejection as placing the case into better form for appeal.

Continuing Obligations

It is noted that the examiner has reminded applicant and applicant acknowledges the continuing obligation under 37 CFR 1.178(b) to timely apprise the Office of any prior or concurrent proceeding in which patent no. 5,688,651 is or was involved, and the continuing obligation under 37 CFR 1.56, to timely apprise the Office of any information that is material to patentability of the claims under consideration in the reissue application.

Supplemental Reissue Declaration

Applicant recognizes its obligation to file a supplemental reissue declaration stating that every error

which was corrected in the reissue application not covered by a prior declaration submitted in the application arose without any deceptive intention on the part of the applicant. Such a supplemental reissue declaration will be filed as soon as allowable subject matter is noted in the case.

Written Description Rejection

Claims 177 and 210-228 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The examiner states that the recitation of an antibody capable of inhibiting aggregation of soluble β-amyloid in a subject to an extent at least as great as that obtainable with antibody AMY-33 does not meet the written description provision of 35 USC 112, first paragraph, because there is insufficient guidance and direction of the genus of antibodies broadly encompassed by the claimed invention. The examiner states that, contrary to applicant's assertions that the presently claimed invention is consistent with the claims of example 13 of the PTO's written description training materials, the claims do not recite any actual binding specificity for the claimed antibody or fragments thereof. The claims only recite functional properties. The examiner states that, as broadly interpreted, the immunogen is not limited to the peptide and thus other immunogens may be present in addition to a peptide consisting of Aβ 1-28. The examiner states that the art well recognizes that antibodies possess the ability to react specifically and selectively with

the antigenic determinants or epitopes eliciting their production. The examiner states, however, that the instant claims do not recite such antigen specificity. The examiner states that the claims broadly encompass any peptide sequence capable of inhibiting β-amyloid aggregation and/or disaggregated β-amyloid aggregates and such a genus is not clearly supported by the specification. This part of the rejection is respectfully traversed.

In an attempt to obviate this part of the rejection and at least place the claims into better form for appeal, all of the claims have now been amended to specify that the antibodies and the fragments thereof bind β-amyloid. Applicant had thought that this was implicit in the claims and a required construction thereof. Nevertheless, applicant is happy to make this an explicit part of the claims. It is not believed that this type of rejection was previously made or such an amendment would have been earlier. As this part of the amendment places the claims in better form for appeal, entry at this stage of the prosecution is respectfully requested. As indicated above, in a telephone interview, the undersigned was informed that the present amendment would be entered for the purpose of appeal.

Furthermore, the language about being obtainable using a certain peptide as an immunogen has been further amended to specify that the immunogen consists of the peptide. Thus, the claims can no longer be read with the broad interpretation made by the examiner for the first time in this

rejection, i.e., that they read on the possible presence of other immunogens and that the antibody may be binding to the other immunogen and not to the peptide of residues 1-28 of β-amyloid. The present amendment now makes explicit that the β-amyloid peptide fragment is the only immunogen that is present and that the antibodies bind to β-amyloid. As this part of the amendment also places the claims in better form for appeal, entry at this stage of the prosecution is respectfully requested. As indicated above, in a telephone interview, the undersigned was informed that the present amendment would be entered for the purpose of appeal.

With these amendments, it is clear that the present claims should be free of any 35 USC 112 rejection for the same reasons as stated with respect to Example 13 of the written description training materials and as discussed in applicant's previous amendment, which arguments are incorporated herein by reference. Reconsideration and withdrawal of this part of the rejection are therefore respectfully urged.

The written description rejection further states that, with respect to claims 177 and 210 to 218, the claims broadly recite a therapeutic composition comprising a genetically engineered antibody or fragment thereof that inhibits aggregation of β-amyloid or maintains the solubility of β-amyloid to an extent at least as great as that obtainable with antibody AMY-33 and is obtainable using a peptide consisting of residues 1-28 of β-amyloid as an immunogen. The examiner states that the language about inhibiting aggregation

to an extent at least as great as that obtained with antibody AMY-33 would imply the use and possession not only of antibodies having anti-aggregating abilities the same as that of the mAb AMY-33 but also of antibodies having anti-aggregating properties exceeding that AMY-33. Therefore, the claims are drawn to a genus of genetically engineered antibody having a degree of functional activity equal to or greater than the functional activity of AMY-33. The examiner states that the specification does not provide guidance or support for a class of antibodies determined to meet or exceed the functional ability of the antibody AMY-33 to inhibit β-amyloid aggregation. The examiner states that applicant has only demonstrated one species within the genus, which species uses AMY-33, and this does not constitute a representative number of species such that one would recognize that applicant was in possession of the invention as broadly claimed. The examiner states that the skilled artisan cannot envision the detailed chemical structure of the encompassed genetically engineered antibodies. This part of the rejection is respectfully traversed.

Contrary to the examiner's statement, the present specification does provide support or guidance for classifying antibodies based upon a particular level of functional activity. Example 2 in the present specification shows that monoclonal antibody AMY-33 prevents self-aggregation in the presence or absence of heparan sulfate and/or metal ions. On the other hand, monoclonal antibody 6F/3D was ineffective

without the presence of Zn^{2+} and even then was only partially effective. Clearly, therefore, the specification does provide classification based on a level of functional activity. Negligible activity, such as that obtained with mAb 6F/3D was clearly distinguished from the good prevention of aggregation shown by mAb AMY-33. These antibodies were clearly classified based on a particular level of functional activity.

Previously, the claims read on all levels of functional activity, thus reading on the genus that includes AMY-33 - and all other antibodies raised against the claimed immunogen or recognizing the claimed sequence - which bind to β-amyloid and which inhibit aggregation or induce disaggregation. The claims now only read on those antibodies that have the functional activity of AMY-33 or better. Just as applicant was in possession of the entire genus prior to the amendment limiting to the activity of AMY-33 or better, so applicant was in possession of the subgenus which eliminates all those antibodies that have an activity less than that obtainable with AMY-33. Reconsideration and withdrawal of this part of the rejection is therefore also respectfully urged.

Claims 177 and 210-218 have been rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement because new matter is presented. The examiner states that there is no support in the specification as originally filed for anti-β-amyloid antibodies that inhibit aggregation of β-amyloid to a

particular specified degree, much less one that is described in terms of meeting or exceeding the ability of the antibody AMY-33 to inhibit β-amyloid aggregation. The examiner states that there is neither verbatim support for the new claim language nor does it flow naturally from the disclosure as originally filed. The examiner states that the specification does describe any assay that could be used to test the anti-aggregating abilities of candidate antibodies and compare them directly to that AMY-33. The examiner states that the disclosure of a preferred embodiment usually implies the highest or best embodiment achievable or known to applicants at the time of filing. This rejection is respectfully traversed.

First of all, the examiner is incorrect in stating that the specification does not contain an assay for comparing the anti-aggregating abilities of candidate antibodies. Figures 7A and 7B show the result of an assay that compares the anti-aggregating properties AMY-33 and 6F/3D. Particularly, the second bar of section 1 of these two figures quantitatively show that AMY-33 has a much greater ability to prevent aggregation than 6F/3D. This same assay may be used to compare any two antibodies.

The written description guidelines set forth in MPEP 2163 state at section I B:

> While there is no *in haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure.

Here, the newly added claim language is supported in the specification through implicit or inherent disclosure. The concept of the use of any antibody that binds to Aβ and prevents aggregation is present in the present specification as filed, for example, at column 16, line 21-26. Furthermore AMY-33 was indicated as being a preferred embodiment in that same passage. While the examiner states that it must be presumed that AMY-33 is as good as it gets, one of ordinary skill in the art reading the present specification would not believe that. It can be seen that the specification describes testing on Aβ of only two antibodies having the required epitope specificity. One of those two was much better than the other one and was thus indicated as being preferred. However, no one of ordinary skill in the art would have considered that, once one raises and tests other antibodies for these properties, other antibodies having properties even better than those shown in the assay of Figure 7A might be found.

Accordingly, the present specification contains the generic concept of all antibodies that bind β-amyloid and inhibit aggregation or cause disaggregation of β-amyloid and are either obtainable by using a particular fragment of Aβ as an immunogen or recognizing a particular epitope of Aβ. This includes the entire range of anti-aggregating. Additionally, the specification teaches the specific anti-aggregating activity shown in Figure 7A for AMY-33. Thus, there is implicit or inherent support for that range beginning at the

activity of AMY-33 shown in Figure 7A and higher. In this regard, note MPEP 2163.05 III, relating to range limitations, where it states:

> With respect to changing numerical range limitations, the analysis must take into account which ranges one skilled in the art would consider inherently supported by the discussion in the original disclosure. In the decision in *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976), the ranges described in the original specification included a range of "25%-60%" and specific examples of "36%" and "50%". A … limitation to "between 35% and 60%" did meet the description requirement.

By that logic, the range from that amount of activity possessed by AMY-33 (see Figure 7A(1)) and higher, is inherently supported by the disclosure of the full range of activities that include an activity barely above negligible to the highest amount possible, in combination with the specific example with the number shown in Figure 7A(1). Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 177, 210-213 and 215-217 have been rejected under 35 USC 103(a) as being unpatentable over Bickel and in view of Becker and Ladner. The examiner states that Bickel teaches monoclonal antibody AMY-33 and its use as an *in vivo* diagnostic. The examiner states that Bickel suggests the use of monoclonal antibodies for therapeutic use in the last sentence thereof. The examiner cites Becker and Ladner for desirability of genetically engineering an antibody intended

for therapeutic use to make it into a single chain antibody. The examiner states that applicant's previous arguments are not persuasive because, while diagnostic use of AMY-33 antibody is one utility suggested by Bickel, Bickel also suggests that humanized monoclonal antibodies or antibodies having reduced immunogenicity could be used therapeutically. This rejection is respectfully traversed.

The last paragraph of Bickel begins with the statement that the "^{111}In-labeled cationized AMY-33 has been developed as a tool for radioimmunoimaging of cerebral amyloid deposits using SPECT technology." The paragraph then goes on to state that other antibodies may be evaluated as diagnostic tools. The paragraph then continues with a discussion of the generalities of antibodies used for *in vivo* diagnostic tools, stating that it is desirable to diminish their immunogenicity. The paragraph then concludes with the sentence:

> Therefore, the "humanization" of murine monoclonal antibodies prior to mAb cationization may facilitate the use of these proteins as neurodiagnostic or therapeutic agents in humans (49).

The paper cited as reference 49 is Partridge, W.M. (1991) *Peptide Drug Delivery To The Brain*, pp. 235-236, Raven Press, New York. This is clearly a generic book about peptide drug delivery to the brain and is applicable to any antibody that one wishes to use as neurodiagnostic or therapeutic agents in humans. One of ordinary skill in the art reading the entirety of Bickel would never believe that this last sentence, which

is really a generic statement applicable to all antibodies that can be used either as neurodiagnostic or a therapeutic agent in humans, contains a suggestion that AMY-33 has any properties that would make it useful as a therapeutic agent. This sentence is not a suggestion that the specific antibody AMY-33 is useful as a therapeutic agent in humans. If it were such a suggestion, this would be a *non-sequitur* as the rest of Bickel gives no suggestion that there might be any possible therapeutic use for AMY-33. Certainly, there is no enabling disclosure in Bickel for any kind of therapeutic use for AMY-33.

The only disclosed *in vivo* use for this antibody is as a diagnostic after it has been labeled with a radiodetectable marker. Thus, the examiner's basis for this rejection, i.e., that one of ordinary skill in the art would find it obvious to use AMY-33 as a therapeutic, simply fails as there is absolutely nothing in Bickel which would suggest this. The reference to therapeutic agents in humans in the last sentence of Bickel clearly is a generic statement relating to any antibody that may be used as a neurodiagnostic or a therapeutic agent. It would not be considered by one of ordinary skill in the art as a disclosure that AMY-33 might be used as a therapeutic agent, particularly in the absence of any suggestion of why or how it could be said as such. Accordingly, reconsideration and withdrawal of this rejection is respectfully urged.

Claims 177, 210-213, 215-217, 219-223, and 225-227 have been rejected under 35 USC 103(a) as being unpatentable over Walker as evidenced by Hanan and Solomon and Bacskai in view of Becker. The examiner states that Walker suggests that antibody 10D5 may be employed to deliver therapeutic agents directly to Aβ in the brain. The examiner states that Walker, in light of the other evidence, establishes that the antibody thereof has all of the claimed limitations except that it is not genetically engineered, such as into a single chain antibody. The examiner states that Becker discloses that anti-β-amyloid antibodies useful for the treatment of Alzheimer's disease may be genetically engineered. The examiner concludes that it would have been obvious at the time the invention was made to genetically engineer the 10D5 monoclonal antibody to create a less immunogenic antibody molecule, such as a single chain antibody, for use in therapeutic applications as taught by both Walker and Becker. This part of the rejection is respectfully traversed.

Just as with Bickel, Walker does not teach any therapeutic use for antibody 10D5. While Walker suggests that there may be therapeutic utility for an antibody that can bind to β-amyloid in the brain in order to deliver therapeutic agents that could prevent or reverse Aβ deposition in the brains of patients with cerebral vascular amyloidadois or Alzheimer's disease, Walker does not teach that any such therapeutic agents exist.

Furthermore, even if such therapeutic agents existed, Walker does not teach that antibody 10D5, when bound to such therapeutic agents, would still bind to β-amyloid *in vivo*. This general disclosure of Walker is only a recognition that, if such therapeutic agents against amyloid deposition were ever discovered in the future, then antibody 10D5 might be of interest as a research tool to try to deliver those therapeutic agents to the brain. But Walker certainly provides no present motivation for one of ordinary skill in the art at the time the present invention was made to humanize antibody 10D5 or to make it into a single chain antibody. Becker only suggests that this would be obvious to do with an antibody known to have some type of therapeutic utility. Such was not known for antibody 10D5 at the time the present invention was made.

The only utility for antibody 10D5 taught by Walker is a diagnostic utility in combination with imaging technology, such as PET or SPECT, to diagnose β-amyloidosis in living subjects. However, PET and SPECT require labeled antibodies and the present claims exclude labeled antibodies. It is true that the experiments of Walker do not use labeled antibodies, but this is only because they were able to remove the brains of the monkeys studied and then label the antibodies with a secondary labeled antibody using PAP and DAB. This is obviously not possible for diagnostic use of such antibodies in humans.

Accordingly, no combination of Walker with Becker teaches or suggests any motivation to genetically engineer the antibody of Walker. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Conclusion

It is submitted that all of the claims now present in case clearly define over the references of record and fully comply with 35 U.S.C. 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By /rlb/
Roger L. Browdy
Registration No. 25,618

RLB:jhw
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528